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Regulatory and Trade
Counsellors

August 22, 1997

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
MD WC-05
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Comments on the NTP's July 11 proposal to upgrade
the listing of 2,3,7,8-TCDD ("dioxin") to "known" carcinogen

The attached comments on this listing proposal make the following points, among others:

- The NTP criteria for the "known" carcinogen category require more than "limited" human evidence.
- IARC recently determined that the human evidence was only "limited".
- NTP never disagrees with IARC evaluations of the human evidence.
- The public has a right to know how and why the internal NTP process nominated TCDD for a listing change.
- This listing nomination should be withdrawn as lacking merit that would warrant further review.

We request that NTP respond to these recommendations prior to further NTP review proceedings.

Sincerely,

Jim J. Tozzi
Director

Attachment

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Comments on the NTP Public Notice of Review of 2,3,7,8-TCDD for Change of Listing to Category of "Known to be a Human Carcinogen" in the *Report on Carcinogens, Ninth Edition* (62 *Fed.Reg.* 37272, July 11, 1997); and Recommendation for Withdrawal of the Review Nomination

August 22, 1997

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We recommend that the subject nomination be withdrawn. It is in clear conflict with the recent IARC Working Group evaluation of the TCDD epidemiologic data as "limited", and there is no reasonable chance that independent NTP review of such data could satisfy the NTP criteria for the "known" category, which requires "sufficient" human evidence--*i.e.*, substantially more than "limited" evidence. It appears that historically NTP has relied on such IARC evaluations and has never listed an agent based on a finding at variance with an IARC evaluation of the human data. Since the February 1997 IARC evaluation there are no new human studies that could be considered sufficient to alter the IARC evaluation, and it has been reported that the IARC Working Group took any significant "in press" human data into consideration.

Reportedly this listing nomination was generated internally (within the NTP BRC committee), rather than through the external petition process. Internal NTP listing nominations should be judged by the same standard applied to external petitions: whether the nomination/petition "warrants formal consideration". However, NTP has not made available to the public any rationale for the nomination that would allow the public to comment on whether there is a sufficient basis for formal consideration of the proposed listing change. Moreover, the IARC Monograph, Vol. 69, on which the nomination is apparently premised, has not been available to the public during the comment period.[1] Continuing the review in the absence of sufficient supporting rationale for the nomination would be a waste of resources for both NTP and the public, and, in the absence of such scientific support, could only be perceived as having other motivations, to the detriment of the National Toxicology BRC program.

I. The February 1997 reclassification of TCDD does not support, and if effect precludes, the proposed NTP listing change.

The NTP criteria for the "known" category require that there be "sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship...." 61 Fed.Reg. 50499-50500, Sept. 26, 1996 (emphasis added).

The terms used in the "known" criteria, including "sufficient" and "indicates", are not defined, but to a large extent their general intent can be gathered from considering them in contrast to the "human data" portion of the criteria for the "reasonably anticipated" category. Those criteria are that there be "limited evidence of carcinogenicity from studies in humans which indicates that causal interpretation is credible but that

[1] Monograph Vol. 69 was not published until August 11 and was not even made available for mailing from IARC headquarters in France until August 18 (and is still not available from U.S. WHO sales offices).

alternative explanations such as chance, bias or confounding factors could not be adequately excluded...." *Id.* (emphasis added). From these criteria, it can be seen that the criteria for "known" must require human evidence which is stronger than that which would only support a "credible" causal interpretation. In other words, the terminology in the criteria for the "known" category, that there be human evidence which "indicates a causal relationship"-- especially when taken together with the title of the category ("known" indicating a very high level of scientific confidence)--should be understood to require that the human evidence be sufficiently strong to establish a causal relationship with a high level of scientific confidence.

A reliable science policy journal (*Risk Policy Report*, Aug. 18, 1997) has reported (copy of article attached) that the 2,3,7,8-TCDD (hereafter simply "TCDD") internal nomination to the "known" category was premised on its being consistent with the February 1997 action by IARC action in upgrading TCDD from its "possibly carcinogenic" category (Group 2B) to its "carcinogenic to humans" category (Group 1). The news report also quoted an NTP spokesperson (Dr. Jameson) as hoping "'to take advantage of Dr. [George] Lucier's expertise and recent experience with the IARC process.'" Dr. Lucier chaired the IARC Working Group that recently upgraded TCDD.[2]

As Dr. Lucier knows, however, and as other NTP committee members should be able to ascertain from the currently available IARC public documents, IARC evaluated the human data as "limited", and not "sufficient" (even when it focused on high-exposure subgroups in occupational cohorts). The February 14 IARC press release (fax and Internet copies attached) stated that "direct epidemiological evidence for these conclusions [that TCDD is carcinogenic to humans] was considered limited"; and the Monograph summary (Internet copy attached) stated that "it was considered that there is *limited evidence* in humans for the carcinogenicity of 2,3,7,8-TCDD." (Original emphasis). The term "limited evidence" in this statement is italicized by IARC because it is a defined term in its Monographs Programme criteria.

The IARC Working Group upgraded TCDD to its Group 1 despite the finding of "limited" human evidence because it used "mechanism of action" data to compensate for the limited human data. However, the NTP criteria (which have been found to be "rules" and are therefore binding on the agency[3]) diverge from the IARC criteria in that the NTP

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[2] Dr. Lucier is not an epidemiologist, however, and expertise in epidemiology is critical to the "known" classification.

[3] Synthetic Organic Chem. Mfrs. Ass'n v. HHS, 720 Fed.Supp. 1244 (W.D.La. 1989).

criteria do not allow "mechanism of action" data to compensate for "limited" human data which are not sufficient to show a causal relationship in order to elevate an agent to the top hazard ranking.[4]

IARC has defined its terminology of "sufficient" and "limited" human data. The IARC definition of "limited" corresponds exactly in substance to the NTP criteria for the "reasonably anticipated" listing category, which hinges on the term "limited", and the IARC definition of "sufficient" also corresponds closely to the NTP usage in the criteria for its category of "known". The IARC Preamble to its Monographs Programme defines "sufficient" and "limited" human evidence as follows:

> The evidence relevant to carcinogenicity from studies in humans is classified [by the Working Group] into one of the following categories:
>
> *Sufficient evidence of carcinogenicity*: The Working Group considers that a causal relationship has been established... That is, ... chance, bias and confounding could be ruled out with reasonable confidence.
>
> *Limited evidence of carcinogenicity*: [A] causal interpretation is considered ... to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence. [Underlining added]

Historically, the NTP has relied consistently on IARC evaluations of the human data in its listing decisions.[5] Its *Seventh Annual Report on Carcinogens (Summary)*, the

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[4] IARC revised its listing criteria to allow for this in 1991. NTP did not make similar revisions when it completed its review of its listing criteria in September 1996. 61 *Fed.Reg.* 50499-50500. However, the revised NTP criteria did allow for mechanism of action data to be used to support an NTP listing of "reasonably anticipated" in cases where there is "less than sufficient evidence of carcinogenicity in humans...." *Id.* Even with the extra latitude in the revised IARC Group 1 criteria, however, the final IARC determination to change the TCDD classification from "possibly carcinogenic" to "carcinogenic" was clearly controversial within the Working Group, since it was approved only by a majority vote of 14-10, and the Working Group appeared to be "stacked" with five U.S. government scientists, three of whom (including Dr. Lucier) are directly and substantially involved in the current attempt to revise the EPA reassessment of risks of dioxin and related compounds to meet with approval from its Science Advisory Board (which would not support the Agency's 1994 proposed re-assessment). Also, a separate International Expert Panel convened by the American Health Association appeared to arrive at a different conclusion in 1996 (see footnote 8).

[5] This may be due to the NTP's concentration on animal bioassay experiments and data and the absence of sufficient epidemiological expertise on its listing review committees. IARC involves substantial epidemiologic expertise in its Monograph Working Groups. The February 1997 TCDD Working Group reportedly had at least eight voting Working Group members who were epidemiologists.

most recent *Report* available (1994), states that "the Annual Report's scheme and associated degrees of evidence are based on IARC's classification scheme and degrees of evidence." At 6. Throughout the *Seventh Annual Report*, the NTP classifications consistently reflect the IARC criteria, and rely almost exclusively on the IARC Working Group evaluations of such data. With the exception of one substance, for which there was not an IARC evaluation, thorium dioxide, all substances in the *Report* that were listed by NTP as "known to be carcinogenic" had been evaluated by IARC Working Groups as having shown "sufficient" evidence of carcinogenicity in humans. All substances classified in the *Report* as "reasonably anticipated are ones that IARC had evaluated as having "limited" evidence for carcinogenicity in humans.[6] This same NTP listing *Report* relied in part on the 1987 IARC finding of no adequate data to evaluate carcinogenicity in humans in making the determination to list TCDD as "reasonably anticipated". At 370. Many of the IARC evaluations of the human data had been conducted five or more years before the *Seventh Annual Report*, and yet there was nothing to indicate that more recent data had been evaluated or even searched for.

In other words, NTP has never, so far as we know (certainly not in the *Seventh Annual Report*) either (1) classified a substance to NTP's category of "known to be carcinogenic" in an instance where an IARC Working Group had found the epidemiologic data to be only "limited"; or (2) diverged from an IARC Working Group evaluation of the epidemiologic evidence. The current nomination of TCDD to the NTP "known" category is clearly at odds with this historical practice and with the recognized consistency between the IARC and NTP criteria terminology of "limited" and "sufficient". To adopt an NTP listing of "known" in the face of the very recent IARC evaluation of the human evidence as "limited" would be highly unusual and questionable, particularly since apparently the IARC reclassification is the primary basis for the listing nomination.

II. The NTP category of "known" indicates a requirement for a higher degree of scientific confidence in causal relationship than the IARC criteria.

Although the IARC Group 1 classification is sometimes referred to as "known human carcinogen" determination, such references are inaccurate. IARC does not use the term "known". Particularly in the scientific community, the term "known" indicates a very high degree of confidence in the weight of the evidence (and certainly something more than

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[6] There were fourteen such substances or groups of substances: acrylonitrile, beryllium, bischloroethyl nitrosourea, cadmium and cadmium compounds, diethyl sulfate, ethylene oxide, formaldehyde (gas), nickel and certain nickel compounds, nitrogen mustard hydrochloride, oxymetholone, phenacetin, phenytoin, silica (crystalline, respirable size), and 2,4,6-trichlorophenol.

simply the "credible" causal "interpretation" used in the NTP criteria for "reasonably anticipated" which incorporate the concept of "limited" human evidence).[7] It is important to consider the plain meaning of words in view of the importance NTP listings have for public perceptions and their influence on regulatory activities.

In a context of applied expert judgment, the plain meaning of "known" transcends opinions for which scientific support is uncertain. The *Random House Dictionary of the English Language* (2d ed. unabridged, 1987) states the primary definition of "know" and "known" as "to perceive or understand as fact or truth; to apprehend clearly and with certainty;...." To anyone familiar with the epidemiologic data on dioxin, attaching to it the term "known to be a human carcinogen" should be obviously inappropriate.[8]

The legislative history materials for the NTP listing program support the premise that the term "known" was intended to denote a high level of scientific confidence in the determination. When the legislation establishing the program was considered and passed by Congress in 1978, the House committee report[9] used the term "confirmed carcinogen" as a synonym for "known carcinogen".[10] When the bill was brought to the floor of the House for the final vote, the distinction between the two categories was explained with the statement that "[t]he report should be properly organized so that no possible confusion

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[7] Absence of the term "known" from the IARC Group 1 criteria apparently allows for high levels of Working Group disagreement over its listing decisions, such as reflected in the 14-10 vote on the recent IARC dioxin reclassification. Such levels of disagreement are not consistent with the certainty indicated by the term "known".

[8] While it might be tempting to draw some support from experimental animal data relevant to TCDD, not only would such be contrary to the NTP listing criteria for "known", it would also be inappropriate in view of the receptor-binding characteristics of TCDD. Receptor-binding agents, or ligands, such as TCDD are notorious for their interspecies variability in endpoint response. See the 1996 special issue of *Pharmacology & Therapeutics* devoted to "Cancer Mechanism and Risk Assessment". One of the ten environmental agents reviewed in the issue was TCDD. The review was overseen by a 19-member "International Expert Panel" (with one additional person who was Liaison from the National Cancer Institute), which was convened by the Amercian Health Association with support from a National Cancer Institute grant. The Expert Panel's Introduction to the chemical-specific reviews states: "Further research is required to determine whether the tumorigenic effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in rodents apply to humans." *Pharm. & Ther.* 71(1/2):1, 4. The special issue's review of TCDD concluded that the epidemiologic studies were inconsistent and showed a potential for differential misclassification and confounding, and therefore they "have not established TCDD as a human carcinogen...." *Id.* at 218. (The chemical-spcecific reviews in the special issue were also supported by the National Cancer Institute grant.)

[9] The 1978 legislation emanated from the House; there is nothing pertaining to the legislation in the Senate report.

[10] H.R.Rep.No. 95-1192 on H.R. 23347, 95th Cong., 2d Sess., Comm. on Interstate and Foreign Commerce, at 28.

could exist between clearly demonstrated carcinogens and those for which convincing data are not yet available...."[11]

III. Human studies published since the February 1997 IARC reclassification do not support the proposed NTP listing change.

The only significant new epidemiologic study published since the February 1997 IARC evaluation and reclassification of which we are aware is the IARC mortality study results published in the June 1997 issue of the *American Journal of Epidemiology*.[12] That study is clearly not adequate to support a revision of the IARC evaluation of the human data from "limited" to "sufficient". The strength of association was very weak (an apparent elevation in relative risk for all cancers combined of only 1.12 from 1.06); there was a potential for confounding and misidentification of underlying disease states; there was potential for exposure misclassification; and association with exposure variables was not consistent. The study authors' conclusions were guarded: They concluded that the study findings indicated that exposure "to herbicides contaminated with dioxin may be associated with a small increase in overall cancer risk and in the risk for specific cancers." (Emphasis added). Several of the study authors (and IARC staff) were part of the IARC February 1997 Working Group and were undoubtedly familiar with this data, which was finalized and in press by that time.

Conclusion

There is no apparent scientific rationale for the proposed change in NTP listing, and the NTP has not provided any on which the public can comment. The recent IARC Working Group evaluation of the TCDD human data, which is what NTP usually relies on, determined the human data to be "limited" and thus appears to preclude the NTP review in view of the consistency between the NTP and IARC listing terminology, the almost complete reliance which NTP has placed on IARC epidemiologic evaluations in the past, and the lack of any persuasive new data since the IARC evaluation. The TCDD nomination should be withdrawn as soon as possible as lacking in sufficient merit in order to save NTP and the public the time and expense of a futile review (just as an outside petition would be returned under similar circumstances) and in order to avoid a perception

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[11] Cong.Rec. of Oct. 10, 1978, H-34938.

[12] Kogevinas M, Becher H, Benn T, Bertazzi PA, Bofetta P, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Fingerhut M, Green L, Kauppinen T, Littorin M, Lynge E, Mathew JD, Meuberger M, Pearce N, Saracci R. "Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins." *Am. J. Epidem.* 145(12):1061-75.

of the nomination as having some motivation other than new scientific knowledge. At the least, a new *Federal Register* notice should be issued for the dioxin nomination, providing the public with rationale for the nomination (including an explanation on how it can be reconciled with the NTP listing criteria and the IARC findings) and extending the comment period in order to allow the public an opportunity to obtain and review IARC Monograph Vol. 69 (if the IARC reclassification is given by NTP as a basis for the nomination).

IARC evaluates carcinogenic risk associated with dioxins

(Issued 14 February 1997)

A Working Group of 25 scientists from 11 countries met at the International Agency for Research on Cancer (IARC) in Lyon during February 4-11, 1997, to review evidence for the potential carcinogenicity of polychlorinated dibenzo-para-dioxins (commonly known simply as dioxins) that exist as environmental contaminants worldwide. The Working Group reviewed all the published scientific data on the occurrence of cancer in human populations that are known to have been exposed to high levels of dioxins as a result of industrial accidents or environmental exposures. They further assessed the evidence for carcinogenic effects of dioxins in experimental animals, and evaluated possible biological mechanisms of carcinogenesis by these substances.

Dioxins are formed as unintended by-products of certain chemical reactions, including those used to produce trichlorophenol and several herbicides. They are exceptionally stable compounds, and therefore persist for long periods both in the environment and in tissues of exposed individuals. Industrial accidents in several countries have caused high exposures to workers, and in one case (in Seveso, Italy, in 1976), to residents of the surrounding area. In some of these incidents there was exposure to 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD), the most biologically potent of the dioxins.

The conclusion of the Working Group was that TCDD is carcinogenic to humans, slightly increasing the overall risk of lung cancer and of all cancers combined, each by a factor of approximately 1.4 in the most highly exposed workers. In comparison, heavy smoking of cigarettes increases lung cancer risk by a factor of approximately 20. While direct epidemiological evidence for these conclusions was considered limited, the Working Group also took into account the fact that TCDD causes cancer in multiple organs in experimental animals; that it has been shown to act in animals by a mechanism that is likely also to operate in humans; and that tissue concentrations of TCDD are similar both in heavily exposed human populations in which an increased overall cancer risk was observed and in rats exposed to carcinogenic doses.

For all other dioxins the evidence at this time was considered to be inadequate for evaluation in human populations and limited or inadequate in experimental animals, and therefore these compounds were evaluated as unclassifiable at present as to their ability to cause cancer in humans.

The results will be published as Volume 69 of the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. This series is recognized internationally as providing unbiased evaluations of chemicals, pharmaceutical agents, complex mixtures, industrial processes and biological and physical agents that could increase the risk of cancer in humans. This process is essentially an identification of carcinogenic hazards and an estimation of the strength of the evidence for such identification. The Monographs do not attempt quantitative risk assessments or risk-benefit determinations and are not intended as a basis for regulatory actions.

For more information, please contact Dr Douglas McGregor, or click below:

- ☐ Polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans (Vol. 69) *Available July 1997 (c. 700 pages) ISBN 92 832 1269* X

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International Agency for Research on Cancer

PRESS RELEASE

WHO

N° 115 14 February 1997

IARC EVALUATES CARCINOGENIC RISK ASSOCIATED WITH DIOXINS

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IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Polychlorinated Dibenzo-*para*-dioxins and Polychlorinated Dibenzofurans (Vol. 69)

Available July 1997, advance orders accepted now.
ISBN 92 832 1269 X

The *IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans* convened a meeting of 25 experts from 11 different countries in Lyon, France during 4-11 February, 1997, to evaluate the evidence for polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) being risk factors for human cancer. Although quantitative information, including dose-response relationships, were important in reaching the conclusions of the meeting, **the question of quantitative risk estimation was not addressed.** This meeting was the third time at which these substances were considered within this programme. In 1977 few data were available and no evaluation of chlorinated dibenzo-*p*-dioxins could be made, either on the basis of animal carcinogenicity evidence or reports of people exposed to contaminated herbicides (*IARC Monographs* Vol.15). By 1987 the animal carcinogenicity data had developed to the stage where there was *sufficient evidence* in experimental animals for the carcinogenicity of 2,3,7,8-TCDD, but the epidemiological evidence remained *inadequate*. Accordingly, at that time, 2,3,7,8-TCDD was classified in Group 2B, *possibly carcinogenic to humans*; all other PCDDs were classified in Group 3, *not classifiable as to carcinogenicity to humans* (*IARC Monographs* Supplement 7).

Occurrence

PCDFs are formed as inadvertent by-products in the production and use of polychlorinated biphenyls (PCBs) and, in combination with PCDDs, in the production of chlorophenols and have been detected as contaminants in these products. PCDFs and PCDDs also may be produced in thermal processes such as incineration and metal processing and in the bleaching of paper pulp with free chlorine. PCDFs also are found in residual waste from the production of vinyl chloride and the chloralkali process for chlorine production. The relative amounts of PCDF and PCDD congeners produced depend on the production or incineration process and vary widely.

PCDDs and PCDFs are ubiquitous in soil, sediments and air. Excluding occupational or accidental exposures, most human exposure to PCDDs and PCDFs occurs as a result of eating meat, milk, eggs, fish and related products, as both PCDDs and PCDFs are persistent in the environment and accumulate in animal fat. Occupational exposures to both PCDDs and PCDFs at higher levels have occurred since the 1940s as a result of production and use of chlorophenols and chlorophenoxy herbicides and to PCDFs in metal production and recycling. Even higher exposures to PCDDs have occurred sporadically in relation to accidents in these industries. High exposures to PCDFs have occurred in relation to accidents such as the Yusho (Japan) and Yu-cheng (Taiwan) incidents involving contamination of rice oil and accidents involving electrical equipment containing PCBs.

In human tissues, current mean background levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD, or 'dioxin', the PCDD that has caused most concern) are in the range of 2-3 ng/kg fat and the sum of the penta- and hexa-chlorinated PCDF congeners commonly found in human tissues is generally in the range 10-100 ng/kg fat. Accidental exposures to high levels of PCDDs or PCDFs have led to increases in tissue concentrations above these background levels of up to four orders of magnitude for TCDD and one or more orders of magnitude for PCDFs. Because of the long half-lives of many of these substances in humans (e.g., ca. 7 years for TCDD), a single, acute exposure from the environment results in the exposure of potential target tissues for a period of years.

Human carcinogenicity data

PCDDs. The most important epidemiological studies for the evaluation of 2,3,7,8-TCDD are four cohort studies of herbicide producers (one each in the United States and the Netherlands, two in Germany). These studies involve the highest exposures to 2,3,7,8-TCDD. The cohort of residents in a contaminated area from Seveso, Italy is well known, but the exposures at Seveso were lower and the follow-up shorter than those in the industrial settings. Most of the four industrial cohorts include analyses of sub-cohorts considered to have the highest exposure and/or longest latency. Additional studies of herbicide applicators, both cohort and case-control studies, and military personnel in Viet Nam who have considerably lower exposures to 2,3,7,8-TCDD, were not considered to be critical for the evaluation.

http://www.iarc.fr/publications/vol69.htm

Overall, the strongest evidence for the carcinogenicity of 2,3,7,8-TCDD is for all cancers combined, rather than for any specific site (average relative risk ca. 1.4). An increased risk of lung cancer, with about the same relative risk, is also present in the most informative studies. There are few examples of agents which cause an increase in cancers at many sites; an important example is tobacco smoking (for which, however, there are clearly elevated risks for certain specific cancer sites). This lack of precedent for a multi-site carcinogen without particular sites predominating means that the epidemiological findings must be treated with caution. On the basis of this information, it was considered that there is *limited evidence* in humans for the carcinogenicity of 2,3,7,8-TCDD. There was *inadequate evidence* in humans for the carcinogenicity of PCDDs other than 2,3,7,8-TCDD.

PCDFs. Two incidents, each involving about 2000 cases, occurred in which people were exposed to sufficient PCBs and PCDFs to produce symptoms. Fatal liver disease is 2-3 times more frequent than national rates in both cohorts. In Japan, at 22 years of follow-up, there is a three-fold excess of liver cancer mortality in men, which was already detectable and even higher at 15 years of follow-up. In Taiwan, after 12 years of follow-up, there is no excess of liver cancer mortality. Based upon these data, it was concluded that there is *inadequate evidence* in humans for the carcinogenicity of PCDFs.

Animal carcinogenicity data

PCDDs. In a number of experiments with rats and mice in which 2,3,7,8-TCDD was administered, increases in the incidence of liver tumours was consistently found in both males and females. In addition, tumours were increased at several other sites in rats, mice and Syrian hamsters, but these effects were dependent upon the species, sex and route of administration of 2,3,7,8-TCDD. Although the doses resulting in increased tumour incidence in rodents are extremely low, they are very close to doses that are toxic in the same species. These data led to the conclusion that there is *sufficient evidence* in experimental animals for the carcinogenicity of 2,3,7,8-TCDD.

Evaluation of much smaller databases led to the conclusion that there is *limited evidence* in experimental animals for the carcinogenicity of a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-HxCDD and that there was *inadequate evidence* for the carcinogenicity in experimental animals of 2,7-dichloroDD, 1,2,3,7,8-pentachloroDD and 1,2,3,4,6,7,8,-heptachloroDD.

PCDFs. There are no long-term carcinogenicity studies on PCDFs, but some tumour promotion studies were evaluated in which rats and mice were exposed to some of the congeners following short duration exposure to known carcinogens. It was concluded that there is *inadequate evidence* in experimental animals for the carcinogenicity of 2,3,7,8-TCDF, but there is *limited evidence* in experimental animals for the carcinogenicity of 2,3,4,7,8-pentaCDF and 1,2,3,4,7,8-hexaCDF.

Other evidence

The toxicity of 2,3,7,8-TCDD segregates with the cytosolic aryl (aromatic) hydrocarbon receptor (AhR), and the relative toxicities of other PCDD congeners is associated with their ability to bind to the receptor, which occurs in all rodent and human tissues. The AhR binding affinities of 2,3,7,8-TCDF, 1,2,3,7,8- and 2,3,4,7,8-pentaCDFs are in the same order of magnitude as that observed for 2,3,7,8-TCDD. PCDDs with at least three lateral chlorine atoms bind with some affinity to the AhR. Current evidence is that most, if not all, biological effects of 2,3,7,8-TCDD and other PCDDs arise from an initial high affinity interaction with the AhR and it appears that the biochemical and toxicological consequences of PCDF exposure are the result of a similar mode of action. The limited carcinogenicity data available for congeners other than 2,3,7,8-TCDD indicate that carcinogenic potency is also proportional to AhR affinity. Based on this evidence, all PCDDs and PCDFs are concluded to act through a similar mechanism and require an initial binding to the AhR. Binding of 2,3,7,8-TCDD to the AhR results in transcriptional activation of a battery of 2,3,7,8-TCDD-responsive genes, but currently no responsive gene has been proven to have a definitive role in its mechanism of carcinogenesis.

Overall evaluation

Taking all of the evidence into consideration, the following evaluations were made:

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) *is carcinogenic to humans (Group 1).*

The Working Group took into consideration the following supporting evidence:

(i) 2,3,7,8-TCDD is a multi-site carcinogen in experimental animals that has been shown by several lines of evidence to act through a mechanism involving the Ah receptor;

(ii) this receptor is highly conserved in an evolutionary sense and functions the same way in humans as in experimental

animals;

(iii) tissue concentrations are similar both in heavily exposed human populations in which an increased overall cancer risk was observed and in rats exposed to carcinogenic dosage regimens in bioassays.

Other polychlorinated dibenzo-*p*-dioxins *are not classifiable as to their carcinogenicity to humans (Group 3).*

Dibenzo-*p*-dioxin *is not classifiable as to its carcinogenicity to humans (Group 3).*

Polychlorinated dibenzofurans *are not classifiable as to their carcinogenicity to humans*

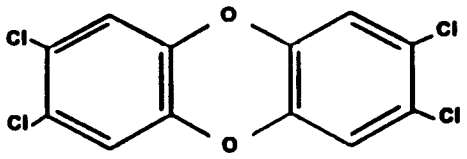
(Group 3).

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

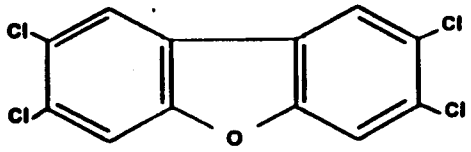
- 2,3,7,8-TCDD was recommended for possible listing in the 9th Report on Carcinogens (RC) by the NIEHS RC Review Committee.

- The nomination took into account the IARC classification of TCDD as a Group 1 "Known Human Carcinogen" (IARC Monograph Vol 69, 1997).

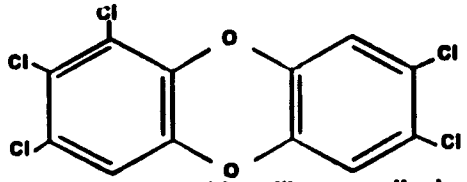
Selected polychlorinated dibenzo-p-dioxin, polychlorinated dibenzofuran and polychlorinated byphenyl congeners



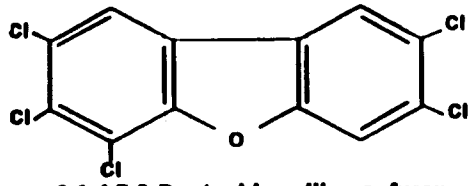
2,3,7,8-Tetrachlorodibenzo-p-dioxin



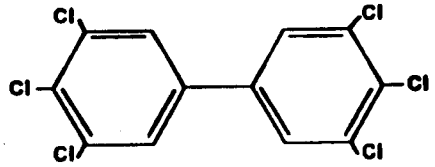
2,3,7,8-Tetrachlorodibenzofuran



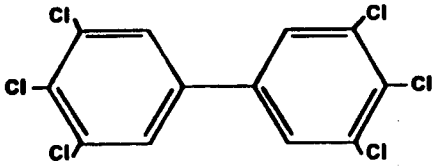
1,2,3,7,8-Pentachlorodibenzo-p-dioxin



2,3,4,7,8-Pentachlorodibenzofuran



3,3',4,4',5,5'-Hexachlorobiphenyl



3,3',4,4',5-Pentachlorobiphenyl

Sources of dioxins

Unwanted contaminants:

Incineration--including municipal solid waste, toxic waste and hospital incinerators

Some herbicides and pesticides

Paper and pulp bleaching with chlorine

PCB transformer fires

Metal smelting

Leaded gasoline emissions

Cigarette smoke

Polyvinyl chloride (PVC) manufacture and fires

Other/unknown

(Small amounts manufactured for scientific research)

Exposure information

Intake:

Human intake of dioxins in the U.S. occurs universally, beginning prior to birth.

Human tissue levels, U.S. Adults:

2,3,7,8-TCDD in adult blood, milk or adipose tissue lipid is approximately 3 ng/kg (ppt).

Total dioxin toxic equivalents (TEQ) in U.S. adult blood lipid is approximately 20-60 ppt.

Total estimated dioxin body burden in U.S. adults is approximately 13 ng/kg TEQ.

Estimated adult dioxin tissue levels after special exposures are 96-97,000 ng/kg BW TEQ.

General population exposure: 95+% from food (meat, dairy and fish)

Special exposures: Occupational or environmental (chemical workers, Seveso)

Case-control studies: Selected cancers associated with exposure to phenoxy-herbicides, chlorophenols, and/or dioxins

- Soft-tissue sarcoma
- Non-Hodgkin's lymphoma
- Hodgkin's disease
- Leukemia
- Nasopharynx & nasal cancer
- Prostate cancer
- Multiple myeloma

Summary of the combined international cohort and selected industrial cohort studies with high exposure levels

Part I: All Cancers

Reference	Cancer Deaths	SMR	95% CI
International (IARC) Cohort			
Kogevinas et al. (1997)	394	1.2	1.1 – 1.3
Industrial Populations (high-exposure subcohorts)			
Fingerhut et al. (1991a) (USA)	114	1.5	1.2 – 1.8
Becher et al. (1996) (Germany)	105	[1.3]	[1.0 – 1.5]
Hooiveld et al. (1996a) (Netherlands)	51	1.5	1.1 – 1.9
Ott & Zober (1996) (BASF, accident)	18	1.9	1.1 – 3.0
Total	**[288]**	**[1.4]**	**[1.2 – 1.6]**
p value			< 0.001

[Calculated by the IARC Working Group]

After IARC Monographs on the evaluation of the carcinogenic risks to humans: polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans. World Health Organization (69), 1997.

Summary of the combined international cohort and selected industrial cohort studies with high exposure levels

Part II: Lung Cancers

Reference	Cancer Deaths	SMR	95% CI
International (IARC) Cohort			
Kogevinas et al. (1997)	127	1.2	1.0 – 1.4
Industrial Populations (high-exposure subcohorts)			
Fingerhut et al. (1991a) (USA)	40	1.4	1.0 – 1.9
Becher et al. (1996) (Germany)	33	[1.4]	[1.0 – 2.0]
Hooiveld et al. (1996a) (Netherlands)	14	1.0	0.5 – 1.7
Ott & Zober (1996) (BASF accident)	7	2.4	1.0 – 5.0
Total	**[94]**	**[1.4]**	**[1.1 – 1.7]**
p value			< 0.01

[Calculated by the IARC Working Group]

After IARC Monographs on the evaluation of the carcinogenic risks to humans: polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans. World Health Organization (69), 1997.

Summary of the combined international cohort and selected industrial cohort studies with high exposure levels

Part III: Non-Hodgkin lymphoma

Reference	Cancer Deaths	SMR	95% CI
International (IARC) Cohort			
Kogevinas et al. (1997)	14	1.6	0.9 – 2.7
Industrial Populations (high-exposure subcohorts)			
Fingerhut et al. (1991a) (USA)	2	0.9	0.1 – 3.4
Becher et al. (1996) (Germany)	6	[4.6]	[1.7 – 10.0]
Hooiveld et al. (1996a) (Netherlands)	3	3.8	0.8 – 11.0
Total	**[11]**	**[2.6]**	**[1.3 – 4.7]**
p value			< 0.01

[Calculated by the IARC Working Group]

After IARC Monographs on the evaluation of the carcinogenic risks to humans: polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans. World Health Organization (69), 1997.

Summary of the combined international cohort and selected industrial cohort studies with high exposure levels

Part IV: Soft-tissue sarcoma

Reference	Cancer Deaths	SMR	95% CI
International (IARC) Cohort			
Kogevinas et al. (1997)	3	2.3	0.5 – 6.6
Industrial Populations (high-exposure subcohorts)			
Fingerhut et al. (1991a) (USA)	3	9.2	1.9 – 27.0
Becher et al. (1996) (Germany)	0	0.0	–
Hooiveld et al. (1996a) (Netherlands)	0	0.00	–
Total	**[3]**	**[4.7]**	
p value			

[Calculated by the IARC Working Group]

After IARC Monographs on the evaluation of the carcinogenic risks to humans: polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans. World Health Organization (69), 1997.

15-year cancer mortality follow-up study of Seveso accident

	Cancer Deaths			
	Observed	Expected	RR	95% CI
Zone A (16 total cancer deaths)				
Females -- Digestive System	5	3.3	1.5	0.5 – 3.5
Males -- none remarkable				
Zone B (152 total cancer deaths)				
Females -- Myeloma	4	0.6	6.6	1.8 – 16.8
Males -- Rectum	7	2.4	2.9	1.2 – 5.9
Males -- Lymphohemopoietic	12	5.1	2.4	1.2 – 4.1
Zone R (1,007 total cancer deaths)				
Females -- Bone	7	2.9	2.4	1.0 – 4.9
Males -- Soft Tissue Sarcoma	4	1.9	2.1	0.6 – 5.4

Source: Bertazzi, P.A. et al. Dioxin exposure and cancer risk: A 15-year mortality study after the "Seveso Accident." Epidemiology 8:646-652, 1997.

Cancer mortality follow-up of occupationally exposed Dutch cohort

	Observed Cancer Deaths	SMR	95% CI
All Male Workers (N=549)			
All Malignant Neoplasms	51	1.5	1.1 – 1.9
Urinary Organs	8	3.9	1.7 – 7.6
Non-Hodgkin's Lymphoma	3	3.8	0.8 – 11.0
Male Workers Exposed to TCDD in Accident (N=140)			
All Malignant Neoplasms	20	1.7	1.1 – 2.7
Prostate	3	5.2	1.1 – 15.3
Non-Hodgkin's Lymphoma	1	3.9	0.1 – 21.8

Source: Hooiveld, M. et al. Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. American Journal of Epidemiology (accepted for publication, 1997).

Sites of TCDD carcinogenicity in laboratory animals

Nose
Palate
Tongue
Lung
Liver
Skin
Thyroid
Hematopoietic (lymphoma, multiple myeloma, leukemia)
Connective and soft tissue
Total tumors

Summary of experimental carcinogenesis studies in laboratory animals

TCDD causes cancer in multiple species, multiple strains, both sexes, and multiple organs and tissues

TCDD causes cancer by multiple routes, various durations of exposure, and ranges of exposure concentrations

Species and strains:

- Mice: Swiss, B6C3F1, B6C
- Rats: Sprague-Dawley, Osborne-Mendel
- Hamsters: Syrian golden

Routes of exposure: feed, oral (gavage), dermal, injection

Treatment with a known carcinogen followed by chronic treatment with TCDD

- Rat liver +
- Mouse skin +

The aryl hydrocarbon (Ah) receptor and TCDD

- The scientific consensus is that binding to the Ah receptor is a necessary early step for all known TCDD effects.

- The Ah receptor is found in the cytoplasm of vertebrate cells from fish to humans.

- The Ah receptor has similar properties in humans and laboratory animals.

Selected molecular and biochemical responses following TCDD binding to the Ah receptor

- There are numerous Ah receptor mediated responses that have been characterized in experimental systems.
- Many of these responses are relevant to plausible mechanisms of chemical carcinogenesis.
- In every case, where these responses have been observed in humans or human cells, results indicate qualitative and quantitative similarity between rodents and people.

Selected toxic responses associated with dioxin exposures

Response	Species
Cancer	Human Hamster Rat Mouse
Non-Cancer	
Chloracne	Human Monkey Rabbit Mouse
Decreased birth weight	Human Rat Hamster
Decreased testosterone	Human Rat
Altered glucose homeostasis	Human Guinea pig Rat

Half-lives of elimination of 2,3,7,8-TCDD in humans and rodents

Rats, mice, hamsters	**2-4 weeks (usually)**
Humans	**5.8 - 11 years**

Comparison of dose response across species requires consideration of the extraordinary persistence of TCDD in people.

Arguments for listing 2,3,7,8-TCDD as a Known Human Carcinogen

- Studies in humans including two new studies following IARC review of TCDD strongly point to a causal association between exposure to TCDD and an increased incidence of cancers in highly exposed occupational cohorts.

- All cancer rodent studies of TCDD have been positive. These studies involve multiple species, multiple strains, both sexes and multiple organs. These studies also involve multiple routes of exposure.

- Mechanistic studies support a common mode of action for TCDD in humans and rodents.

- Body burdens necessary to produce dioxin mediated responses are similar in rodents and people.

Arguments against listing 2,3,7,8-TCDD as a known human carcinogen

- Humans, including occupational cohorts exposed to dioxins, are also exposed to mixtures of other carcinogenic substances.

- The human cancer data alone may not be sufficient to establish causality between dioxin exposure and human cancer.

Review Group 1 and Review Group 2 Recommendations for 2,3,7,8-TCDD

- The NIEHS Review Group 1 voted unanimously (10:0) to recommend that 2,3,7,8-TCDD be listed in the 9th Report on Carcinogens as *known to be a human carcinogen.*

- The NTP Executive Committee Working Group (Review Group 2) voted unanimously (8:0) to recommend the listing of 2,3,7,8-TCDD in the 9th Report on Carcinogens as *known to be a human carcinogen.*